

INFLUENZA EPIDEMIC

The most unusual features so far of the influenza epidemic are the season at which it has come and the ages of the few patients reported to have died of it. The great infectivity of the Asian virus in a world population lacking antibodies against it no doubt accounts for its rapid spread here at a season when the incidence is normally low. The notable feature of the deaths that have been attributed to it is the relatively high proportions of schoolchildren and middle-aged adults. The very young and the very old seem not to be succumbing in the proportions that past experience would suggest as usual. The case fatality rate is evidently exceedingly low, at least at present, and reports of the disease from abroad do not suggest that a high rate is to be expected. In its progress across the country the disease has occasionally received such publicity as might be the envy of an invading army from Mars. But many doctors will agree with the general practitioners whose letters appear at p. 763 that, if exaggerated, this can do more harm than good.

Reports of the disease¹⁻⁵ have not disclosed any particularly unusual signs or symptoms. The first of these reports, from Malaya,¹ was written partly by a general practitioner, so that symptoms of milder cases not admitted to hospital receive due emphasis. The authors of the report stated that "recovery is usual by the fourth day," experience which the medical officer of Aden confirms.³ They mentioned thirst as being an early symptom, followed in 6-12 hours by sore throat. In contrast, a high incidence of sore throat was not noted in a report from Kuwait,² though it was described as characteristically red, dry, and mat in another from the same area.³ The familiar aches and pains, malaise, and shivering that make the influenza victim a miserable object seem to be as common in this outbreak as in others. In Holland antibodies to the Asian strain have been found in people aged 80 to 90, suggesting a possible if somewhat remote virological relationship with an epidemic that spread from Asia in 1889-90.³

Of two deaths reported at Kuwait,⁵ middle-aged Indian men, one was considered to be due to secondary bronchopneumonia and the other to primary influenzal pneumonia with pleural effusion. Some cases of secondary bronchopneumonia in Great Britain are considered to be due to a staphylococcus, and the possibility is being investigated of an association between secondary bronchopneumonia and skin infection in the patient or members of his family. Treatment on the normal lines seems to be effectual, for few complications are reported. As to a preventive vaccine, not enough is likely to be available to stem the tide of infection, though selected groups of people, including doctors, are being or soon will be offered it. A vaccine can give only incomplete

protection, perhaps about 30-40% if the results of the Medical Research Council's studies of other influenza vaccines may be taken as a guide,⁶ though a protection of about 70% has been attained under the restricted conditions of the U.S. armed forces.⁷ At present there seems no reason to depart from the view expressed in these columns recently that, so long as the Asian influenza remains mild, vaccination of the general population is unnecessary and perhaps unwise.⁸ Indeed, immunization is still an experimental procedure.⁹

With each batch of vaccine being distributed by the Ministry of Health will go a pamphlet giving technical details, including information on possible reactions and contraindications. Tried out on civilian and military volunteers, the vaccine has not been found to cause serious reactions; some cases of sore arm have been noted, and slight malaise for 24 hours. About 3-4% of subjects have also experienced headache and slight pyrexia. Contraindications include a history of epilepsy, allergic diseases, and sensitivity to egg.

Since influenza is not a notifiable disease, the medical officer of health is specially dependent on the willing help of his medical colleagues in general practice and hospitals for the running of an efficient intelligence service during an epidemic. In accordance with previous practice,¹⁰ the medical officer of health usually asks certain general practitioners to act as "spotters" and keep him informed of the first signs of an outbreak, but he will welcome information from general practitioners not so designated. In addition, local officers of the Ministry of Pensions and National Insurance are informing medical officers of health when sickness benefit claims either increase by 30% over the figure for the previous week or are double the average weekly figure for the period April 4 to December 4, 1956. These measures should help to give some idea of how the disease spreads through the country, and they show that at present it is mainly in the northern half of England and South Wales. The incidence of cases cannot be known. The spread of infection has been very rapid in eastern countries, and, if it runs true to form here, may almost have subsided by the turn of the year. A second outbreak, caused by one of the older virus strains, might then appear in what we have come to regard as the true influenza season.

WASP STINGS

We have learnt a good deal in recent years about stings. Nettle stings owe their effects to the presence of histamine, acetylcholine, and hydroxytryptamine in them.¹⁻³ Thus the nettle produces its effects by injecting substances present in man's own body. A much more serious matter is the wasp, for the effects of its sting last for several days and are occasionally fatal; two deaths are reported in our medico-legal column at page 771 this week.

In 1949 F. C. MacIntosh and W. D. M. Paton⁴ described a new class of compounds called "histamine liberators." Histamine is liberated in anaphylaxis, and anaphylaxis was discovered during a study of extracts of the stinging tentacles of sea anemones. Therefore in 1954 R. Jaques and M. Schachter⁵ investigated sea

¹ Smith, C. E. G., Turner, L. H., and Helliwell, C. J. V., *British Medical Journal*, 1957, 1, 1412.

² McCreadie, D. W. A., *ibid.*, 1957, 2, 684.

³ Mulder, J., *Lancet*, 1957, 2, 334.

⁴ Fawcett, A. L., *ibid.*, 1957, 2, 335.

⁵ Guthrie, J., Forsyth, D. M., and Montgomery, H., *ibid.*, 1957, 2, 590.

⁶ M.R.C. Committee on Clinical Trials of Influenza Vaccine, *British Medical Journal*, 1957, 2, 1.

⁷ Burney, L. E., *J. Amer. med. Ass.*, 1957, 164, 2029.

⁸ *British Medical Journal*, 1957, 2, 38.

⁹ *ibid.*, 1957, 1, 1517.

¹⁰ *Monthly Bull. Minist. Hlth Lab. Serv.*, 1956, 15, 226.

anemones to see if they contained a histamine liberator in their tentacles, since when applied to man these tentacles cause cutaneous reactions. They found that an extract of tentacles did in fact release histamine when injected into the fluid perfusing the skin of the cat, and having made this observation they wondered whether the venom of the wasp might also possess similar activity.

In their first paper on wasp venom⁶ they showed not that it released histamine but that it contained both histamine and hydroxytryptamine, and a third substance which they did not identify. (Some samples of wasp venom contained a histamine liberator and also hyaluronidase.) The average weight of the venom sac together with glands was 0.8 mg., and the average histamine content was 3.2 μ g. as determined by quantitative pharmacological tests. This is a large amount. Both histamine and hydroxytryptamine were identified by paper chromatography. Schachter and E. M. Thain⁷ then examined the third and more important constituent present in large quantity, which they called kinin. It appeared to be a polypeptide, a highly potent substance which produced a characteristic delayed contraction of the isolated guinea-pig ileum and a fall of blood pressure in the cat and the rabbit. Recently D. J. Holdstock, A. P. Mathias, and Schachter⁸ have purified kinin and shown that it is exceedingly effective in enhancing capillary permeability. They gave intradermal injections to guinea-pigs and rabbits, followed by intravenous injection of a dye, pontamine blue. Kinin was ten times more effective than histamine in causing increased permeability to the dye in the guinea-pig, and 100 times more effective in the rabbit. Like other polypeptides kinin caused cutaneous pain when it was applied to the base of a blister according to the method of D. Armstrong and colleagues.⁹ In these respects kinin was similar to kallidin, a substance released from the globulin fraction of serum by an enzyme kallikrein present in human saliva, and also similar to bradykinin, which is released from serum by an enzyme in the venom of the snake *Bothrops jararaca*. Thus we see that human saliva has similarities to snake venom and to wasp venom. It is therefore interesting to note that in 1260 Barthelmy de Glanville said that the saliva of the young man has a secret corrupting power, "for if a man is wounded and you put saliva in the wound it corrupts the blood. This is why archers moisten their arrowheads with saliva, for they are more harmful to their enemies." The main damage inflicted by the wasp sting, the oedema of which may persist for two or three days, seems then to be due to the polypeptide kinin. The occasional deaths which are caused, however, are probably not due to kinin but are rather anaphylactic, and arise because of earlier sensitization to wasp venom.

THE BRITISH NATIONAL FORMULARY

It is now eight years since the first edition of the now familiar *National Formulary* appeared. Fathered by the B.M.A. and the Pharmaceutical Society of Great Britain, with the co-operation of the Departments of Health and the Service Departments, this enterprise occupies an established place in medical practice, providing doctors and pharmacists with a selection of formulae and preparations comprehensive enough to meet all the ordinary needs of general medicine. Though the *N.F.* was in many respects the direct successor of the *National War Formulary*, the Joint Formulary Committee set up in 1946 to prepare the first volume was faced with a far more onerous task than that which faced those who prepared the *N.W.F.*, largely because the imminence of the National Health Service foreshadowed a big switch from private to Health Service prescribing. The committee, therefore, submitted their ideas for comment to a large number of bodies representing the medical and pharmaceutical professions before they finally committed themselves to print.

The fifth edition of the *Formulary*¹ was published in August and comes into operation on November 1. The customary title of *National Formulary* has now been discarded for that of *British National Formulary* because, it is said, there was evidence of some confusion of the old name with that of the *National Formulary, U.S.A.*, which is a book of standards. In the latest edition some of the older and familiar prescriptions have had to give place to new. On the other hand, the committee has kept to its policy of retaining preparations or formulae still being widely used or frequently prescribed even if their justification on pharmacological grounds is open to dispute. The *B.N.F.* does not hold itself out to be a textbook, and the committee is right to cater for the practitioner's natural conservatism in prescribing, which certainly springs as much from a fund of practical experience as it does from habit.

The Joint Formulary Committee this year has embarked on a new venture, foreshadowed in the preface to the 1955 *N.F.*, in the shape of an alternative addition² to the *B.N.F.* in which the preparations are grouped according to their pharmacological use instead of alphabetically, and in which English titles replace Latin. After making inquiries the committee believed that there would be a demand for the new volume, particularly from hospitals for teaching purposes. In general the contents of the alternative edition are the same as that of the main edition and the formulae are identical. Each group of drugs is preceded when practicable by a short account of the actions and uses of the preparations which follow, and these descriptive monographs replace the prescribers' notes, although in some cases they are the same. The alternative edition will not be distributed free of charge by the Departments of Health to doctors in the National Health Service as has been done with the main edition, and what demand

¹ Emmelin, N., and Feldberg, W., *J. Physiol.*, 1947, **106**, 440.

² Collier, H. O. J., and Cheshier, G. B., *Brit. J. Pharmacol.*, 1956, **11**, 186.

³ *British Medical Journal*, 1956, **2**, 595.

⁴ MacIntosh, F. C., and Paton, W. D. M., *J. Physiol.*, 1949, **109**, 190.

⁵ Jaques, R., and Schachter, M., *Brit. J. Pharmacol.*, 1954, **9**, 49.

⁶ ——— *ibid.*, 1954, **9**, 53.

⁷ Schachter, M., and Thain, E. M., *ibid.*, 1954, **9**, 352.

⁸ Holdstock, D. J., Mathias, A. P., and Schachter, M., *ibid.*, 1957, **12**, 149.

⁹ Armstrong, D., Keele, C. A., Jepson, J. B., and Stewart, J. W., *Nature (Lond.)*, 1954, **174**, 791.

¹ *British National Formulary 1957*. B.M.A. and Pharmaceutical Society of Great Britain, London. Price 6s. 6d.

² *British National Formulary 1957: Alternative Edition*. B.M.A. and Pharmaceutical Society of Great Britain, London. Price 7s. 6d.

there will be for it remains to be seen. One thing that the grouping of formulae in the alternative edition clearly shows is the large number of preparations in the *B.N.F.* that have a similar pharmacological action.

CANCELLOUS STRIP GRAFTING

An innovation in the technique of bone-grafting for non-union and for delayed union of fractures seems likely to be generally adopted. The use of massive cortical grafts is declining. The recent vogue for grafting stored homogeneous bone, which never attained more than a limited popularity in Britain, is passing, at least so far as the treatment of fractures is concerned. Techniques employing the grafting of calf bone have not been accepted outside the Continent of Europe.

Cancellous "strip" grafting, in which the grafts are prepared as flat strips cut from the crest of the ilium, promises to become the standard method in treating indolent fractures. The technique is simple, and, since it employs only spongy bone, has a better physiological basis, because the revascularization and reossification of spongy bone is a much more rapid process than is the incorporation of massive portions of cortex. This new technique appears to have been adopted in many centres simultaneously, mainly as an application of the ideas put forward by D. B. Phemister.¹ The subject was discussed at the spring meeting of the British Orthopaedic Association last May. J. N. Wilson described its application in 22 cases. As with other techniques, the most satisfactory results are obtained in delayed union rather than in established non-union. If the fracture under treatment is stable, by reason either of firm fibrous union or of previous metallic internal fixation, all that is necessary is to refresh the cortex above and below the level of fracture, and to apply strips of iliac cancellous bone to the bared surfaces. External splintage is essential. If the fracture is unstable or badly displaced it must be "taken to pieces," reduced, fixed with a plate and screws or with an intramedullary nail, and the cortex refreshed and grafted similarly.

There is nothing new in reliance upon grafts of cancellous bone rather than upon cortex. W. E. Gallie in 1931² and H. Matti in 1932³ demonstrated the greater osteogenetic powers of grafted cancellous bone, and cancellous "chip" grafts have been widely used ever since, both for slow union of fractures and in operations for intra-articular arthrodesis. Strip grafting has the advantages over chip grafting that a larger bone-producing area is produced and that it is often possible to leave the fracture itself undisturbed.

Strip grafting alone, even reinforced with internal fixation, is seldom adequate for the treatment of non-union with considerable gap between the fragments. In such cases the method combining the use of a block of cancellous bone with internal fixation, as advocated by E. A. Nicoll,⁴ is an advance over previous techniques. If, however, bone has not been lost and there is no gap

between the fragments, cancellous strip grafting is so simple and so certain that it should be employed early, as soon as it becomes apparent that a fracture of the shaft of an adult bone is not healing properly and is likely to present the problem of delayed union. Some orthopaedic surgeons would go further, advocating the use of this method as a primary procedure in comminuted fractures or in fractures inflicted by major violence in which, for any reason, open reduction and internal fixation are to be employed.

RENAL CALCULI IN SEVERE PARALYSIS

A dangerous complication for the severely paralysed patient is the development of renal calculus. It is apt to occur because the calcium balance is disturbed. In the normal subject osteoblastic and osteoclastic activity are about equal, but in the patient with severe paralysis the balance is upset. The stress that muscles exert on bone is a stimulus to osteoblastic activity, and in the severely paralysed patient it is missing. In consequence, osteoclastic activity continues, but osteoblastic activity is diminished. Calcium is therefore lost from the bones, and the excess is excreted in the urine. In severe cases of acute poliomyelitis the calcium balance becomes negative early in the paralytic stage of the disease, and becomes increasingly so until it reaches a plateau after about five weeks. Loss of calcium continues at this level for some months, and equilibrium is not again attained for about seven months.¹ During this period the hypercalciuria may be sufficient to cause a calculus to form; this is more likely to occur if the urine becomes alkaline owing to urinary infection, excessive artificial respiration, or ingested alkali.

When sodium phytate is taken by mouth it forms the insoluble calcium phytate, and prevents the calcium being absorbed from the alimentary tract. P. R. Vagelos and P. H. Henneman² have recently investigated the effect of this substance on the urinary excretion of calcium in severely paralysed patients. Their nine patients were quadriplegic owing to poliomyelitis and had hypercalciuria. They were given two courses of sodium phytate, the first lasting about six weeks, the second about four weeks. In five of the nine patients the urinary excretion of calcium fell appreciably during treatment, and the decrease in hypercalciuria suggests that sodium phytate deserves further trial in the prevention of renal calculi in these patients. The dosage has to be restricted lest it cause diarrhoea.

The measures commonly recommended to prevent the formation of renal calculi are a generous fluid intake, avoidance of urinary infection, especially by scrupulous sterility in catheterization, and frequent changes of posture. The last does not affect calcium metabolism,³ but may be useful in preventing stagnation of urine in the renal pelvis. These measures, important though they are, have not solved the problem, and further progress may depend on reducing the amount of calcium in the diet or making it unavailable by giving sodium phytate.

¹ Phemister, D. B., *J. Bone Jt Surg.*, 1947, **29**, 946.

² Gallie, W. E., *British Medical Journal*, 1931, **2**, 840.

³ Matti, H., *Arch. klin. Chir.*, 1932, **168**, 236.

⁴ Nicoll, E. A., *J. Bone Jt Surg.*, 1956, **38B**, 70.

¹ Whedon, G. D., and Shorr, E., *J. clin. Invest.*, 1957, **36**, 966.

² Vagelos, P. R., and Henneman, P. H., *New Engl. J. Med.*, 1957, **256**, 773.

³ Whedon, G. D., and Shorr, E., *J. clin. Invest.*, 1957, **36**, 982.